Has Halothane a Predominant Circulatory Action?

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Some circulatory actions of halothane were determined in mongrel dogs. Arterial pressure, cardiac rate and contractile force were directly measured. Ganglionic (stellate) blockade was estimated by comparing chronotropic responses to pre-ganglionic and post-ganglionic stimulation of the cardiac sympathetic nerves. Stroke volume was calculated from the pressure pulse. It was found that halothane caused ganglionic blockade, reduced contractile force, lowered arterial blood pressure, diminished cardiac output, reduced total peripheral resistance, and interfered with the response of myocardial contractile force to stimulation of post-ganglionic sympathetic nerves. The combined effects of ganglionic blockade and direct depression of the myocardial response to sympathetic stimulation were such that the response of contractile force to pre-ganglionic nerve stimulation was almost abolished even by light planes of anesthesia which produced little effect upon ganglionic transmission. On the average, mean arterial blood pressure, ganglionic transmission, contractile force, and the response of force to post-ganglionic stimulation were reduced equally by the administration of halothane. However, in the individual cases studied there was no significant correlation between changes in any two of these variables. It was concluded that there are a variety of actions of halothane, none of which is conspicuously more evident or more important than the others in affecting the circulation.

In 1963 one of us pointed out that the typical circulatory actions of halothane could scarcely occur unless the agent caused sympathetic nervous depression in addition to its actions on cardiac and vascular smooth muscle, and we proposed that inhibition of the vasomotor “center” by halothane constituted an important cause of its autonomic effects. Marked depressant actions in the medulla were subsequently demonstrated by a direct method.*

On the other hand, it is well known that halothane antagonizes the effects of norepinephrine, both in cardiac and in vascular smooth muscle, and there has recently been an attempt to revive the hypothesis that ganglionic blockade is an important means whereby halothane affects the circulation. Thus, there are several autonomic actions of halothane, all of which could contribute to its circulatory effects.

The present study was designed to estimate simultaneously the relative susceptibility of axonal conduction, stellate ganglionic transmission and myocardial contractility to the actions of this anesthetic. The stellate ganglion was selected for study because it is involved in the regulation of myocardial activity while previously reported investigations of halothane have not dealt with ganglia which are important in circulatory regulation. We have concluded that there is no single or predominant cause for the circulatory depression produced by halothane; there are at least five separate causes which interact in such a way that their effects summate.

Methods

Six dogs were studied. They were anesthetized with pentobarbital (20–24 mg./kg. intravenously), the trachea intubated, artificial respiration (Bird Mark 4 semiclosed; O₂ at 5 liters per minute total flow) instituted, and the femoral artery and vein cannulated. The arterial cannula was advanced (roughly 30 cm.) until it lay in the descending aorta about 15 cm. above the bifurcation.

The vagi were divided in the neck. The sternum was split in the mid-line, the pericardium opened, and a calibrated 120 ohm Walton-Brodie strain gauge arch * sutured to

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the anterior wall of the right ventricle. The myocardium between the feet of the gauge was stretched approximately fifty per cent prior to initiating any recordings. The sympathetic chains were dissected free bilaterally from fifth thoracic to second and third thoracic, cut at fifth thoracic, and the white rami divided, with the exception of those connecting with thestellate ganglion, on the side stimulated. On the opposite side, the thoracic chain from fifth to first thoracic was ablated and thestellateganglion excised.

Electrical stimuli (5 msec. pulses, 5–15 volts, 2–9 c.p.s., duration 10 seconds) were applied to the sympathetic chain just proximal to the stellate ganglion and to a post-ganglionic nerve (middle cardiosympathetic) on the same side. Silver bipolar electrodes and a Tektronix pulse generator were used. The voltages employed were supramaximal. The amperage supplied was estimated by measuring the voltage drop across a fixed resistance; this voltage decrement was displayed on a Tektronix Model 502 cathode ray oscilloscope. Amperage changes during or between stimulations served to indicate either anatomical displacement of the nerve fibers or electrical shunting caused by an accumulation of blood near the electrodes.

Cardiac rate was transduced by a tachograph activated by the aortic pressure pulses which were in turn transduced by a Statham strain gauge. These variables, together with contractile force and the stimulus characteristics, were recorded by a Grass polygraph. At the end of each study the tachograph was calibrated using a Tektronix pulse generator.

In most cases gallamine (10 mg. intravenously in repeated doses) was given to prevent movement upon stimulation, and in all cases atropine sulfate (0.4 mg.) was given at half-hourly intervals to prevent cardiac actions caused by stimulation of parasympathetic fibers running with the post-ganglionic sympathetic fibers.

In a typical experiment the response of cardiac rate to stimulation of pre- and post-ganglionic fibers was first observed, and the rate of stimulation adjusted to produce equal and easily measurable effects within the lower part of the range of physiologically occurring frequencies (1–10 impulses/second). Once reproducible responses were obtained, the chest was flooded with mineral oil, and the oil maintained at 37.5 ± 0.5° C. by means of an infrared lamp. Following completion of the control observations (a series of three pre- and post-ganglionic stimulations at two-minute intervals), halothane was admitted to the respired gas mixture from a calibrated Fluotec vaporizer. Stimulations were then repeated at two-minute intervals until there was no further effect (usually within 20 minutes), and the same observations repeated at another concentration of halothane.† Usually the concentration sequence was 0–2–1–0.5–0 per cent halothane, but deviations from this order were occasionally made without discernible effect upon the findings. In calculating the results the findings during the first period of halothane administration were compared with those during the first control period, the last "halothane period" with the second control, and the middle halothane period with the arithmetic mean of the responses during the first and second control periods. At the end of the experiment hexamethonium (50 mg.) was administered intravenously and the response to pre-ganglionic stimulation immediately repeated. This procedure was used to verify that all of the fibers stimulated were pre-ganglionic and that the stellate ganglion was adequately perfused with blood.

In a few preliminary experiments the sympathetically blocked animals were bled in order to discover whether the measurement of isometric contractile force was indirectly affected by the level of arterial pressure. Within the range usually encountered there was no effect, but at the lowest pressures measured, force was increased by as much as one-third. Over-transfusion had an opposite effect, and the

† In some cases end-expired gas samples were obtained and analyzed for halothane. Between 20 and 40 minutes after setting the Fluotec at a given concentration, the alveolar tension of halothane was found to equal 0.6 of that inspired.
somewhat increased. In contrast, both responses were found to be reduced when the pre-ganglionic fibers were stimulated. By comparing the responses of cardiac rate (to pre-ganglionic and post-ganglionic stimulation) with their respective controls, the degree of ganglionic blockade was estimated as 25 per cent. Despite the small degree of blockade, pre-ganglionic nerve stimulation barely affected contractile force.

Figure 2 shows the relative effect of halothane on arterial pressure, on contractile force, on contractile force response to post-ganglionic stimulation, and on ganglionic transmission. Although individual results are widely distributed, the median effect upon all four parameters was indistinguishable. At one per cent (inspired) concentration arterial pressure was 68 per cent, contractile force 61, increment in force due to stimulation 72, and ganglionic transmission 62 per cent of control. Individual values of ganglionic transmission ranged most widely, from 2 to over 90 per cent of control.

One factor which could have increased the variability of the results is the rate of nerve stimulation. Specific ganglionic blocking compounds, such as hexamethonium produce a greater effect at high than at low stimulus frequencies. This phenomenon was not encountered with halothane, since stimulation at different rates (ranging from 1–9 impulses per second) in 3 animals did not alter the degree of blockade (table 1).

Two Per Cent Halothane. These results are also shown in figure 2. The effects of 2 per cent halothane on the four parameters were again identical. The median levels of mean arterial blood pressure, resting contractile force, force increment during post-ganglionic stimulation and ganglionic transmission were, respectively, 39, 38, 23, and 22 per cent of the control level.

1 In most experiments in which the resting rate declined during halothane inhalation there was an increase in the response of cardiac rate to post-ganglionic stimulation. In other words, the standard electrical stimulus tended to produce a constant level of cardiac rate irrespective of the starting level. It was necessary to take this finding into account in estimating the degree of ganglionic blockade from the response to pre-ganglionic stimulation.
In 3 animals the maximal levels of contractile force obtainable from post-ganglionic stimulation were compared before, during, and after the inhalation of 2 per cent halothane for thirty minutes. A typical result is graphed in figure 3. Although it was possible to increase the level of contractile force during the administration of halothane, the maximal response attainable was severely depressed, and stimuli at or above the maximal physiological rate either failed to increase the response further or caused a reduction from the peak level of contractile force. In contrast, the response of cardiac rate was essentially unaltered.

Discussion

Answers to three questions were sought in the present investigation. First, can the hemodynamic effects of halothane be ascribed predominantly to any one site or type of action? Second, what degree of blockade of the stellate ganglia does halothane induce? Finally, is it true for sympathetic nervous stimulation (as it is true for norepinephrine infusion) that halothane can depress myocardial contractility beyond the possibility of effective remedy?

The answer to the first question appears to be “no.” All measured parameters were depressed to an equal degree at both concentrations of halothane. Interestingly, estimates of cardiac output, which the method of Hamilton and associates permits, indicate that total blood flow was far less severely affected than was contractile force, the median reduction in output approximating thirty per cent at 2 per cent inspired halothane concentration (this datum is not shown in the tables). Although it could be argued that this discrepancy merely reflects the error inherent in measuring from the “wrong” (right) ventricle, the similarity of effect upon the left and right ventricles demonstrated previously makes this explanation improbable. It seems more likely that cardiac output is preserved in the face of a marked reduction in contractile force by virtue of an increase in diastolic size (which was evident from simple inspection), thereby tending to restore stroke volume toward normal.§

Table 1. Effects of Stimulus Frequency on the Degree of Ganglionic Blockade Produced by Halothane in 3 Different Animals

<table>
<thead>
<tr>
<th>Animal</th>
<th>Conditions</th>
<th>Transmission as Percentage of Control</th>
<th>$f_1 &lt; f_r &lt; f_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/11/64</td>
<td>2% Hal.; 1, 2, 3 imps./sec.</td>
<td>60</td>
<td>55</td>
</tr>
<tr>
<td>12/25/64</td>
<td>1% Hal.; 3, 6, 9 imps./sec.</td>
<td>60</td>
<td>53</td>
</tr>
<tr>
<td>12/9/64</td>
<td>1% Hal.; 3, 6, 9 imps./sec.</td>
<td>65</td>
<td>64</td>
</tr>
</tbody>
</table>

Means: 61.6, 58.0, 66.0

Significance of differences: None

In all cases frequency $f_2$ is double $f_1$ and $f_1$ is triple $f_1$. Frequency range: 1–9 impulses per second.

Fig. 2. Responses of mean arterial blood pressure, resting (unstimulated) contractile force (arbitrary units), and ganglionic transmission (as per cent of control) to a change in halothane concentration from 1 per cent to 2 per cent halothane are shown. Each symbol represents one animal. The horizontal bars indicate median responses.

§ It must be recognized that the isometric contractile force measurement represents only one point (Po) on the force-velocity curve describing the inotropic state of the myocardium and that this measurement is not influenced by changes in
other factor tending to preserve the level of stroke volume is the marked reduction in aortic pressure. Ordinarily, external cardiac work can be increased by “after loading” (increasing out-flow pressure), but this apparently does not occur during halothane inhalation. Therefore, stroke volume cannot be maintained if aortic pressure remains normal, but may be if marked arterial hypotension occurs. In passing, the disproportionate reduction in mean arterial blood pressure indicates a substantial decrease in total peripheral resistance, thus adding still another circulatory action to those directly measured by us.

The studies of stellate ganglion blockade have yielded results which cast doubt upon the possibility that this (or a similar action exerted elsewhere) can explain the hemodynamic actions of halothane. The scatter in the results appears too great to explain happenings as consistent as the reductions in arterial pressure and contractile force. Moreover, there was usually no relation (in individual experiments) between the degree of blockade and the changes in pressure and force. A similar degree of variability was encountered by Larabee and Holaday in their studies of ether and chloroform. They believed that blockade by an anesthetic was increased when, because of uncontrollable functional or structural reasons, the transsynaptic excitation produced by a test volley was unusually low. Finally, the suggestion of Purchase that blockade of the stellate ganglion might have accounted for our previous results during perfusion of the heart is probably invalid since usually no blockade was observed at one-half per cent halothane (inpired) and since it is inconceivable that the ganglia were exposed to concentrations as great as this in our earlier study.

The ability of post-ganglionic sympathetic stimulation to reverse the myocardial depressant effect of halothane was severely compromised by the inhalation of two per cent halothane. The combined effect of reduced myocardial response to sympathetic stimulation and ganglionic blockade observed at this tension of halothane was such that pre-ganglionic stimulation was only one-tenth as effective in increasing contractile force as it was during the control observations. For this reason the belief that vasomotor center depression by halothane is the most important cause of circulatory depression is difficult to sustain. Instead, the combined effects of central autonomic depression, ganglionic blockade and direct depression of the myocardial and vascular responses to the sympathetic mediator appear to render the relevant homeostatic mechanisms virtually ineffective, thus permitting circulatory depression to occur essentially unopposed by the barostatic reflexes.

With respect to the mechanism of action of halothane on the heart, it has already been noted that the chronotropic actions of norepinephrine are unaffected. Consequently, our results suggest that there is no interference with axonal conduction, with the release of neurotransmitter within the myocardium upon the arrival of nervous impulses, or with the specific (B) cardiac receptors with which the transmitter combines. Instead, some part of
the contractile mechanism or of the excitation-contraction linkage appears to be affected.

The ganglionic actions of halothane, unlike those of specific blocking drugs, were found not to be frequency-dependent in the range from 1–9 impulses per second. Presumably, then, the mode of action of halothane, like that of certain other anesthetics is of a different kind from that of hexamethonium and its congeners. While hexamethonium can be viewed as an acetylcholine antagonist, there is no evidence that this is true of halothane, and certain findings suggest that halothane is almost ineffective in this regard. Instead, halothane may act in a non-specific manner to stabilize the postsynaptic membrane by interfering with sodium permeability.

Summary and Conclusions

Simultaneous estimations of the responses of myocardial contractile force and cardiac rate to pre-ganglionic and post-ganglionic stimulation were carried out in dogs both in the presence and absence of halothane in the inspired atmosphere. Mean arterial pressure was also recorded.

There was no conspicuous quantitative difference in the effects of either 1 or 2 per cent halothane on arterial pressure, myocardial contractile force, ganglionic transmission, or myocardial response to post-ganglionic sympathetic nervous stimulation.

We conclude that there is no single or predominant cause for the circulatory depression produced by halothane. Instead, the combination of central autonomic paresis, ganglionic blockade and suppression of the peripheral actions of the sympathetic transmitter, norepinephrine, effectively robs the sympathetic homeostatic mechanisms of their power and permits an unantagonized and direct depression of vascular and cardiac muscle.

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References